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| 10/549,695      | 05/26/2006  | Yasuhiko Tabata      | 3691-0122PUS1       | 9610             |

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| EXAMINER |
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SASAN, ARADHANA

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| ART UNIT | PAPER NUMBER |
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1615

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| NOTIFICATION DATE | DELIVERY MODE |
|-------------------|---------------|

04/29/2009

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

|                              |                                      |   |  |
|------------------------------|--------------------------------------|---|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>10/549,695 | <b>Applicant(s)</b><br>TABATA, YASUHIKO |  |
|                              | <b>Examiner</b><br>ARADHANA SASAN    | <b>Art Unit</b><br>1615                 |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 24 February 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-6 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 and 3-6 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of Application***

1. The remarks and amendments filed on 01/09/09 are acknowledged.
2. Claim 2 was cancelled. Claims 1 and 3 were amended. New claims 5-6 were added.
3. Claims 1 and 3-6 are included in the prosecution.

### ***Continued Examination under 37 CFR 1.114***

4. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/24/09 has been entered.

### ***Response to Arguments***

#### **Rejection of claim 1 under 35 USC § 102(b)**

5. Applicant's arguments, see Page 5, filed 01/09/09, with respect to the rejection of claim 1 under 35 USC § 102(b) as being anticipated by Ikada et al. (JP 08-325160) and with respect to the rejection of claims 3 and 4 under 35 USC § 102(b) as being anticipated by Chvapil (US 4,485,088) have been fully considered and are persuasive in light of the amendment of claim 1.

Therefore the rejections of 08/27/08 are withdrawn.

However, upon further consideration, a new ground(s) of rejection is made over Tabata et al. (Advanced Drug Delivery Reviews 31 (1998) 287-301).

**Provisional rejections of claim 1 under obviousness type double patenting**

6. Applicant's arguments, see Page 7, filed 01/09/09, with respect to the provisional rejection of claim 1 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/484,023 have been fully considered and are persuasive. Therefore, the rejection of 08/27/08 is withdrawn.

7. In light of the abandonment of Application no. 10/528,998 and Application No. 10/551,497, the rejections over these applications are rendered moot.

***Claim Rejections - 35 USC § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 3 and 5-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Tabata et al. (Advanced Drug Delivery Reviews 31 (1998) 287-301).

The claimed invention is a sustained-release preparation which comprises a drug and a gelatin hydrogel. The drug is impregnated into the gelatin hydrogel through a surface thereof and is maintained in the hydrogel by physiochemical interaction. A concentration gradient of the drug is formed in the hydrogel, the concentration gradient being higher at the surface than in other parts of the hydrogel. The sustained-release preparation is sterile.

Tabata teaches that “when mixed with positively or negatively charged gelatin, an oppositely charged protein will ionically interact to form a polyion complex” (Abstract). “The biodegradable hydrogel matrices are prepared by chemical crosslinking of acidic or basic gelatin and are enzymatically degraded in the body with time. The degradation is controllable by changing the extent of crosslinking, which, in turn, produces hydrogels with different water contents. The time course of protein release is in good accordance with the rate of hydrogel degradation. It is very likely that the protein drug complexed with gelatin hydrogel is released as a result of its biodegradation” (Abstract). The advantages of using a polymer hydrogel for protein release including biosafety and inertness towards protein drugs is disclosed (Page 288, right hand column). Tabata teaches that “for achieving effective protein release, it will be a key strategy to immobilize the protein drug to polymer carrier molecules constituting the hydrogel through some molecular interactions” and that “... stable bonding will occur between the oppositely charged polyelectrolytes, which will not dissociate easily” (Page 288, right hand column). Figure 1 shows protein drug release from a biodegradable polymer carrier on the basis of polyion complexation where “a positively charged protein drug is electrostatically complexed with negatively charged polymer chains, constituting a carrier matrix” (Page 289, left hand column). Biodegradable gelatin is the carrier polymer for the hydrogel (Page 289, right hand column). Preparation and sterilization of the hydrogels is disclosed (Page 290, under “Preparation of gelatin hydrogels”). Injectable shapes of the gelatin hydrogels (i.e., solids) are disclosed (Page 289, under the section “2.2 Injectable matrices”). Various proteins that are used as drugs for the

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polyion complexation are disclosed, including bovine milk lactalbumin and basic fibroblast growth factor (bFGF) (Page 291, under section 3.1. "Polyion complexation in aqueous solution"). "The interaction of protein with gelatin results in protein sorption to the gelatin hydrogel" (Page 292, under section 3.2. "Interaction of protein with gelatin hydrogel"). "It may be concluded that the initial driving force of bFGF sorption to the acidic gelatin hydrogel is electrostatic interaction between the two molecules ..." (Page 293, left hand column). Tabata also teaches that "gelatin hydrogels were subcutaneously implanted into the backs of mice and the weights of the hydrogels were measured at different time intervals to evaluate the time profile of in vivo hydrogel degradation" (Page 293, left hand column, and Fig. 5). In vitro release profiles of bFGF that was incorporated into a gelatin hydrogel through impregnation are disclosed (Page 294, left hand column and Fig. 6). This gelatin hydrogel system prevents the protein drug from denaturing, and the release of the protein "is governed by matrix degradation and hence, the period of protein release can be regulated by changing the rate of hydrogel degradation" (Page 298, left hand column).

Regarding instant claim 1, the limitation of a sustained-release preparation which comprises a drug and a gelatin hydrogel is anticipated by the sustained release of bFGF from gelatin hydrogels, as taught by Tabata (Abstract, Page 288 - right hand column, Page 298 - left hand column). The limitation of the drug that is impregnated into the gelatin hydrogel through a surface thereof is anticipated by the bFGF that was incorporated into a gelatin hydrogel through impregnation, as disclosed by Tabata (Page 294, left hand column and Fig. 6). The limitation of maintaining the drug in the

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hydrogel by physiochemical interaction is anticipated by the ionic interaction of drug and polymer to form a polyion complex, as taught by Tabata (Abstract and Page 291, under section 3.1. "Polyion complexation in aqueous solution"). The limitation of a concentration gradient of the drug in the hydrogel, the concentration gradient being higher at the surface than in other parts of the hydrogel is anticipated by the release of drug from the gelatin hydrogel as a result of its biodegradation, as taught by Tabata (Abstract). Since the protein drug is applied on the surface of the gelatin hydrogel, the concentration of the drug will intrinsically be higher on the surface. The limitation of the sterile sustained-release preparation is anticipated by the sterilization of gelatin hydrogels, as taught by Tabata (Page 290, under "Preparation of gelatin hydrogels").

Regarding instant claim 3, the limitation of a method of sustained release of a drug in vivo comprising administering a sustained-release preparation to a patient in need thereof is anticipated by the in vivo release of bFGF from the gelatin hydrogel, as taught by Tabata (Page 294, right hand column and Page 295, right hand column). The limitation of degradation of gelatin hydrogel in vivo causing more drug to be released from a region of higher drug concentration is anticipated by the release of bFGF from the gelatin hydrogel as a result of hydrogel degradation, as taught by Tabata (Page 294, right hand column). The limitation of the maintenance of the drug in the hydrogel by a physiochemical interaction is anticipated by the polyion complexation, as taught by Tabata (Abstract and Page 291, under section 3.1. "Polyion complexation in aqueous solution"). The limitation of a concentration gradient of the drug in the hydrogel, the concentration gradient being higher at the surface than in other parts of the hydrogel is

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anticipated by the release of drug from the gelatin hydrogel as a result of its biodegradation, as taught by Tabata (Abstract). Since the protein drug is applied on the surface of the gelatin hydrogel, the concentration of the drug will intrinsically be higher on the surface. The limitation of the sterile sustained-release preparation is anticipated by the sterilization of gelatin hydrogels, as taught by Tabata (Page 290, under "Preparation of gelatin hydrogels").

Regarding instant claim 5, the limitation of drug impregnation into the gelatin by ionic bonding is anticipated by the anticipated by the bFGF that was incorporated into a gelatin hydrogel through impregnation (Page 294, left hand column and Fig. 6), and by the ionic interaction of drug and polymer to form a polyion complex, as taught by Tabata (Abstract and Page 291, under section 3.1. "Polyion complexation in aqueous solution").

Regarding instant claim 6, the limitation of the preparation in a solid form is anticipated by the injectable shapes taught by Tabata (Page 290, right hand column).

### ***Claim Rejections - 35 USC § 103***

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tabata et al. (Advanced Drug Delivery Reviews 31 (1998) 287-301) in view of Ueda et al. (US 4,749,574).

The teaching of Tabata is stated above.

Tabata does not expressly teach topical administration of the drug-gelatin hydrogel sustained release preparation.

Ueda teaches sustained release transdermal delivery preparations with skin-compatible bases including hydrogels comprised of water-soluble high polymers like gelatin (Col. 2, lines 30-49).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a sustained release preparation of a drug impregnated in a gelatin hydrogel, as suggested by Tabata, combine it with the transdermal delivery preparation of a gelatin hydrogel, as taught by Ueda, and produce the instant invention.

One of ordinary skill in the art would do this because the use of gelatin hydrogels in administering actives across the skin is known in the art, as evidenced by Ueda (Col. 2, lines 30-49). Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results would have been obvious. Please see MPEP 2141.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 4, the limitation of the topical administration would have been obvious over the use of gelatin hydrogels in administering actives across the skin is known in the art, as taught by Ueda (Col. 2, lines 30-49).

***Conclusion***

13. No claims are allowed.
14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/  
Examiner, Art Unit 1615

/MP WOODWARD/  
Supervisory Patent Examiner, Art Unit 1615